REMARKS

Claims 182-201 are pending in the application.

Rejection of claims 182-201 under 35 U.S.C. § 112, second paragraph

Claims 182-201 were rejected as indefinite. The Examiner stated that

> it is not clear if the intervening sequences between nucleotides 120 and 464 and 519 and 668 and 1059 and 1289 and 1308 and 1784 of SEQ ID NO:1 are essential requirements or not for the claimed probes. For example, while 15 contiguous nucleotides are required, it is indefinite whether a probe in which nucleotides 105-120 of SEQ ID NO:1, with the C of nucleotide 120, was extended one nucleotide to incorporate the G of 464 would fall within the scope of the claim. The metes and bounds of the claims are vague and indefinite.

This rejection is respectfully traversed. The claims are directed to nucleic acid probes and methods of using the probes, wherein the probes comprise at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:1 (methylenetetrahydrofolate reductase), the probe comprising at least one or two of:

(a) nucleotide 120 of SEQ ID NO:1 wherein T is replaced by C;

(b) nucleotide 464 of SEQ ID NO:1 wherein T is replaced by G;

(c) nucleotide 519 of SEQ ID NO:1 wherein C is replaced by T;

(d) nucleotide 668 of SEQ ID NO:1 wherein C is replaced by T;

(e) nucleotide 1059 of SEQ ID NO:1 wherein T is replaced by C;

(f) nucleotide 1289 of SEQ ID NO:1 wherein C is replaced by A;

(g) nucleotide 1308 of SEQ ID NO:1 wherein T is replaced by C; and

(h) nucleotide 1784 of SEQ ID NO:1 wherein G is replaced by A;

or the complement thereof.

The nucleotide variances of the claims specify both a position of the variance and the identity of the base pair replacement at the position. The claims do <u>not</u> encompass probes in

which, e.g., "nucleotide 120 of SEQ ID NO:1 wherein T is replaced by C" as recited in part (a), refers to a C arbitrarily appended to any probe from SEQ ID NO:1, as is implied by the Examiner. The variances of (a) through (h) are defined by their position in the context of a larger nucleic acid sequence, i.e., SEQ ID NO:1, thus the inclusion of the specific position of the nucleotide within SEQ ID NO:1 in the claim. The requirement for the variance to be present in a given position further requires that intervening sequences be present between two or more variances. Probes in which the intervening sequences were not present would not fall within the claims because these probes would not comprise "at least 15 contiguous nucleotides of SEQ ID NO:1" if nucleotides were to be arbitrarily added.

The meaning of the claimed subject matter is also clear in view of the specification. The variance sites in the probes are clearly defined in the context of the surrounding sequence. See, for example, page 15, lines 8- 24 of the specification. At page 15, lines 15-22, it states (emphasis added)

> Thus, in preferred embodiments, the detection of the presence or absence of the at least one variance involves contacting a nucleic acid sequence which includes a variance site with a probe, preferably a nucleic acid probe, where the probe preferentially hybridizes with a form of the nucleic acid sequence containing a complementary base at the variance site as compared to hybridization to a form of the nucleic acid sequence having a non-complementary base at the variance site, where the hybridization is carried out under selective hybridization conditions. Such a nucleic acid hybridization probe may span two or more variance sites.

Thus, probes containing two or more variance sites contain the sequence between the variance sites. Applicant submits that the scope of the claims is clear.

Rejection of claims 182, 188, 190, 192, 198, and 200 under 35 U.S.C. § 102(b)

The Examiner rejected claims 182, 188, 190, 192, 198, and 200 under 35 U.S.C. § 102(b) as anticipated by Rozen et al. (WO 95/33054). The Examiner stated

Rozen et al teach an isolated nucleic acid probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:1 (methylenetetrahydrofolate reductase), the probe comprising nucleotide 120 wherein T is replaced by C (Abstract and Figure 1A).

Rozen et al. discloses a sequence of the methylenetetrahydrofolate reductase (MTHFR) gene in which nucleotide 120 is a C. However, this nucleotide does not correspond to nucleotide 120 of SEQ ID NO:1. Applicant filed a replacement Sequence Listing with the Request for Continued Application on November 13, 2001. Nucleotides 111-130 of SEQ ID NO:1 of this replacement Sequence Listing are as follows (nucleotide 120 is bold and underlined):

CCTGGACCC**T**GAGCGGCATG

Nucleotides 111-130 of the MTHFR gene of Rozen et al. are as follows (nucleotide 120 is bold and underlined):

CACCCCGGG**C**CTGGACCCTG

Rozen et al. does not disclose a probe comprising nucleotide 120 of SEQ ID NO:1 wherein T is replaced by C, because the C at position 120 in Rozen's sequence is not equivalent to position 120 in SEQ ID NO:1 of the present application, as is clear from the surrounding sequence. For the same reason, Rozen et al. does not disclose any of the other variances recited in the claims, namely nucleotide 464 of SEQ ID NO:1 wherein T is replaced by G; nucleotide 519 of SEQ ID NO:1 wherein C is replaced by T; nucleotide 668 of SEQ ID NO:1 wherein C is replaced by T; nucleotide 1059 of SEQ ID NO:1 wherein T is replaced by C; nucleotide 1289 of SEQ ID NO:1 wherein C is replaced by A; nucleotide 1308 of SEQ ID NO:1 wherein T is replaced by C; and nucleotide 1784 of SEQ ID NO:1 wherein G is replaced by A.

Nucleotide 120 of SEQ ID NO:1 of the present application corresponds to nucleotide 129 of SEQ ID NO:1 of Rozen et al. However, Rozen et al. does not disclose the claimed variance at position 129, namely, the replacement of a T with a C. Rozen et al. does not disclose the other claimed variances, even when the adjustment in position numbering is accounted for. Rozen et al. does not disclose any of the claimed variances, therefore Rozen et al. does not anticipate claims 182, 188, 190, 192, 198, and 200.

Rejection of claims 184-187, 189, 191, 194-197, 199 and 201 under 35 U.S.C. § 103(a)

The Examiner rejected claims 184-187, 189, 191, 194-197, 199 and 201 under 35 U.S.C. § 103(a) as obvious over Rozen et al. in view of Haughland et al. and Cohen et al. The Examiner cited Haughland et al. and Cohen et al. because "Rozen et al. do not teach a shorter probe comprising no more than 50-500 contiguous nucleotides and a fluorescent label" and because "Rozen et al. do not teach a probe comprising a peptide nucleic acid."

This rejection is respectfully traversed. As discussed above, Rozen et al. does not disclose a probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:1, the probe comprising at least one of: nucleotide 120 of SEQ ID NO:1 wherein T is replaced by C; nucleotide 464 of SEQ ID NO:1 wherein T is replaced by G; nucleotide 519 of SEQ ID NO:1 wherein C is replaced by T; nucleotide 668 of SEQ ID NO:1 wherein C is replaced by T; nucleotide 1059 of SEQ ID NO:1 wherein T is replaced by C; nucleotide 1289 of SEQ ID NO:1 wherein C is replaced by A; nucleotide 1308 of SEQ ID NO:1 wherein T is replaced by C; and nucleotide 1784 of SEQ ID NO:1 wherein G is replaced by A; or the complement thereof. Haughland et al. and Cohen et al. also do not disclose a probe comprising any of the variances recited in the present claims. Therefore, Haughland et al. and Cohen et al. do not make up for the deficiencies of Rozen et al. Thus, the teachings of Rozen et al., Haughland et al, and Cohen et al., either alone or in combination, fail to teach or suggest the claimed invention.

Applicant asks that the rejection of the claims be withdrawn.

Enclosed is a $465 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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